

USE OF A SUBSTANCE WHICH BINDS TO THE
PERIPHERAL BENZODIAZEPINE RECEPTOR IN
THE TREATMENT OF CUTANEOUS STRESS

The present invention relates to a
5 composition for topical use containing a ligand for
peripheral benzodiazepine receptors.

The invention relates to the use of a
substance which binds specifically to the peripheral
benzodiazepine receptor (PBR) for the manufacture of a
10 composition for the prophylaxis or treatment of
cutaneous stress.

The invention also relates to compositions
containing these substances. These compositions may be
cosmetic or pharmaceutical, and in particular topical
15 dermatological compositions.

The term "cutaneous stress" means the various
situations which may cause damage in particular to the
epidermis, irrespective of the agent causing this
damage. This agent may be inside and/or outside the
20 body, for instance a chemical or free-radical agent or
alternatively an external agent such as ultraviolet
radiation.

The composition according to the invention is
thus intended to prevent and combat skin irritation,
25 dry patches, erythema, dysesthetic sensations,
sensations of heating, pruritus of the skin and/or
mucous membranes, and ageing, and may also be used in
skin disorders such as, for example, psoriasis,

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pruriginous diseases, herpes, photodermatitis, atopic dermatitis, contact dermatitis, lichens, prurigo, pruritus, insect bites, in fibrosis and other disorders of collagen maturation, in immunological disorders or
 5 in dermatological conditions such as eczema.

The PBR ligand, also referred to as "substance", contained in the composition may be a non-peptide compound, a peptide, a cell extract or tissue extract of animal or plant origin or a product obtained
 10 by fermenting a microorganism, for example fermenting a bacterium or fungus.

Many PBR ligands are disclosed in the literature. Examples which may be mentioned include Ro 5-4864 or chlorodiazepam, Ro 5-2807 or diazepam and
 15 PK 11195, or reference may be made to the article Peripheral Benzodiazepine Receptors, Ch. III, J.J. Bourguignon, Ed. E. Giesen - Crouse, Academic Press.

PBR is an 18-kd protein located on the outer membrane of the mitochondria of peripheral tissues. It
 20 consists of five transmembrane domains and of a carboxy-terminal portion directed towards the cytosol. Several functions are attributed to PBR depending on the nature of the tissue under consideration: regulation of steroidogenesis, biosynthesis of heme,
 25 cell differentiation and growth, control of mitochondrial respiration (Krueger KE, Biochimica and Biophysica Acta 1995, 1241, 453-470). Although its precise function has not yet been fully elucidated,

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several recent experimental data suggest that PBR might play a fundamental role in regulating the processes of programmed cell death and in protection against free radicals.

5 It has been shown that PBR is in fact closely associated at the mitochondrial level with apoptosis regulatory proteins such as Bcl2 which prevents rupture of the mitochondrial membrane potential, thus preventing the apoptosis induced in particular by the
10 production of reactive oxygenated radicals
(Marchetti P. et al., J. Exp. Med. 1996, 184, 1155-1160); (Marchetti P. et al., J. Immunol. 1996, 157, 4830-4836).

 In the context of the present invention, the
15 protective role of PBR against free radicals was directly observed on cells of hematopoietic origin for which a close correlation between the PBR density and the protection against free radicals was demonstrated. Furthermore, in this same study, it was demonstrated
20 that the transfection of PBR into cells lacking this receptor gives protection against the damage caused by oxygenated species (Carayon P. et al., Blood 1996, 87, 3170-3178).

 Several literature data suggest that PBR
25 might play an important role in regulating apoptosis processes and in protecting cells against damage caused by free radicals.

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Recent phylogenic studies reinforce this novel notion that PBR acts as an apoptosis modulator involved in antioxidant functions. The reason for this is that significant similarities exist between PBR and the protein CrtK of *Rhodobacter sphaeroides*, a photosynthetic bacterium. This bacterial protein which functions as a photosensitive oxygen detector, regulates the expression of the genes involved in photosynthesis in response to environmental changes in oxygen tension and in light intensity. The comparison between PBR and CrtK reveals 35% identity and a conservation of sequence between these two proteins which diverged in the phylogeny two billions years ago. This homology suggests a highly specialized and conserved function of PBR which appears to be similar to that of CrtK in the bacterium. Specifically, it has recently been demonstrated that mammalian PBR transfected into *Rhodobacter* CrtK mutants complements the oxygen-detecting function of CrTK. Thus, this study suggests a key role of PBR in the transduction of oxygen-dependant signals (Yeliseev AA., et al., Proc. Natl. Acad. Sci. 1997, 94, 5101-5106).

However, to date, no substance has ever been precisely indicated as a specific ligand for cutaneous PBR receptors, which is all the more reason why no topically active substance which binds specifically to the PBR receptors has ever been disclosed in the literature.

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It has now been shown, in the context of the present invention, that PBR is abundantly expressed in the skin within the various cell compartments of which it is composed: keratinocytes, Langerhans cells, hair follicles and endothelial cells of the dermal vascular system. In the skin, the expression of PBR follows an increasing gradient from the basal layer to the horny layer. This noteworthy organization which favors the differentiated cells of the epidermis that are the most exposed to external stresses is undoubtedly of primordial physiological importance for protecting the most vulnerable areas of the epidermis. Subcellular studies performed by confocal microscopy indicate, as expected, a colocalization of PBR with Bcl2 in the mitochondrion. Histological studies on skin sections have revealed a surprising distribution of PBR (Figures 1 and 2).

Specifically, the expression of this receptor in the epidermis follows a gradient of increasing density from the basal layers to the most differentiated layers of keratinocytes. This highly organized spatial distribution which favors, in terms of density, the outermost and thus the most exposed cells of the epidermis, leads to the assumption that PBR in the skin might represent a natural protection system against free radicals generated by exposure to ultraviolet radiation. The concomitant observation that the distribution of the anti-apoptotic protein Bcl2

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obeys a strictly inverse gradient suggests a compensatory role of PBR in preserving the cells that are most differentiated.

This set of data which suggest a protective
5 function of PBR, more particularly in the epidermis,
has led to the discovery of natural or synthetic
ligands, showing that their interaction with PBR could
be beneficial in various situations of cutaneous stress
induced by chemical or free-radical agents or
10 alternatively following an exposure to UV.

Thus, according to one of its aspects, the
present invention relates to the use of a ligand which
is specific for PBR, Ro 5-4864, in cutaneous stress.
This ligand is a PBR agonist.

15 According to another aspect of the invention
and on the basis of these observations, a screening
directed toward finding natural PBR ligands was
undertaken and made it possible to isolate several
fractions capable of interacting with this receptor.
20 The potentially protective effect of these natural
ligands was then evaluated in various tests inducing a
cutaneous stress and in particular in tests of
cutaneous erythema induced by UV irradiation. Radical-
scavenging properties and skin repair capacities were
25 also investigated.

Biochemical and pharmacological tests were
used to demonstrate the activity and advantage of the
substances in various situations of cutaneous stress.

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The tests performed with PBR were aimed at showing its potential involvement in regulating apoptotic processes and in preserving skin cells against various deleterious stress situations.

5 **EXAMPLE 1**

Immunohistological studies of cutaneous localization of PBR

A Western blot analysis made it possible to demonstrate the abundant presence of PBR on six
10 different lines of human keratinocytes and on normal human skin (Figure 1), using specific anti-PBR antibodies Ac 8D7 (anti-PBR mouse mAb, isotype IgG1, Dussossoy et al., Cytometry, 1996, 24:39-48). At the subcellular level, the analyses performed by confocal
15 microscopy confirm a colocalization of PBR at the mitochondrial level in keratinocytes (Figure 2).

An immunohistological study performed on a normal human epidermal section using the same antibody reveals a very particular organization since the
20 expression of PBR increases from the *stratum basale* to the *stratum corneum*. This receptor is thus abundantly present on the keratinocytes that are most differentiated, located directly under the *stratum corneum* (Figure 3).

25 **EXAMPLE 2**

Binding and specificity studies

The binding studies were performed on the keratinocyte line A-431 (human epidermoid carcinoma

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FOI b5 b7C b7E b7F b7G b7H b7I b7J b7K b7L b7M b7N b7O b7P b7Q b7R b7S b7T b7U b7V b7W b7X b7Y b7Z

(ATCC, CRL-1555)) by displacement of the reference ligand [^3H]-PK11195. Scatchard analysis indicates a single binding site, a density of about 470 000 receptors per cell and high affinity of the ligand (KD = 1.5 nM) (Figure 4). The specificity of the binding to the peripheral receptor borne by the keratinocytes is confirmed by the pharmacological studies which show a decreasing efficacy of the displacement of the reference peripheral ligand (PK 11195) by the following ligands:

Ro 5-4864 = ($\text{IC}_{50} \approx 25 \text{ nM}$) > diazepam ($\text{IC}_{50} \approx 100 \text{ nM}$) >>> clonazepam (inactive at 3 200 nM). It is recalled that this last compound is a ligand of the central receptor for benzodiazepines, diazepam is mixed and Ro 5-4864 is specific for PBR (Figure 5).

EXAMPLE 3

Involvement of PBR in protection against oxygenated radicals

Two types of experiment are described in Figure 6. The first consists in comparing different lines of lymphoid or myeloid origin as regards their ability to withstand the toxicity of oxygenated radicals in relation with their level of expression of PBR. The results indicate a very strong correlation between the number of PBR sites per cell and the resistance to the toxicity induced by H_2O_2 . There is also a similar correlation when, this time, the level of expression of Bcl2, a protein known to protect cells

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against oxidative damage, is considered. These data, combined with the fact that Bcl2 and PBR are proteins located on the outer mitochondrial membrane, suggest that they may have common functions in cell protection. Interestingly, although the expression of PBR follows a density gradient which increases from the basal layer to the limit of the horny layer, the literature data indicate an inverse phenomenon for the expression of Bcl2, suggesting that during the differentiation of keratinocytes, PBR may take over from Bcl2 as regards the functions of protection against free radicals.

In the second experiment, the possible role of PBR in protection against the toxicity of free radicals is reinforced by the demonstration of the better viability, in the presence of H_2O_2 , of PBR+ transfected Jurkat cells in comparison with homologous PBR- cells.

EXAMPLE 4

The anti-apoptotic activity of the active agents was measured on human keratinocytes and on fibroblasts (ATCC) which were inoculated in 35 mm Petri dishes (5×10^5 cells/well) in DMEM (Dubelco's Mode Eagle Medium) supplemented with 10% fetal calf serum and left to proliferate to the point of confluence. This culture medium is then drawn off, the cells are rinsed and 0.1% fetal calf serum is added in the presence of a saline solution. Increasing concentrations of the substance to be studied are

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added. Twenty four hours later, the apoptosis is measured with an ELISA (enzyme-linked immunosorbent assay) assay kit.

Keratinocytes were subjected to ultraviolet radiation of type B (UVB) at a dose of 250 J/m^2 for 16 hours (J. Invest. Dermatol. 1995, 104: 922-927). In the presence of the PBR ligand Ro 5-4864, it was shown that the cell impairment processes induced by the irradiation are prevented in a ligand concentration range of between 10 nM and $10 \mu\text{M}$.

EXAMPLE 5

The photoprotective effect of the ligand was evaluated by cutaneous application to albino guinea pigs.

The cutaneous topical route is used in order to reproduce the conditions of utilization in man.

Harley guinea pigs, from Charles River France, Saint Aubin les Elbeuf, 76410 Cléon, France, are used.

The animals were shaved and the hair on the right and left hind flanks was then plucked 24 hours before the start of the treatment.

The animals were irradiated immediately before the first treatment. The energy is checked before each irradiation performed on the right and left flanks, in the UVB spectrum at a dose of 4000 mJ/cm^2 .

The right flank of the animals was treated with 0.2 ml of ligand solution immediately after

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irradiation and then 2 and 5 hours after irradiation.
The left flank will not be treated.

A Xeron high pressure vapor lamp (IDEM 300)
will produce the irradiation.

5 The local reactions are read before treatment
and then 5 and 24 hours after irradiation.

Erythema and edema were evaluated as follows:

Erythema

0 no erythema; 1 very mild, barely perceptible
10 erythema; 2 distinct, pale pink erythema; 3 distinct,
bright red erythema; 4 particularly intense erythema

Edema

0 no edema; 1 very mild edema (barely visible); 2 mild
edema (contours well defined and swelling apparent); 3
15 moderate edema (thickness of about 1 mm); 4 serious
edema (thickness greater than 1 mm and area greater
than the area of application).

Examples of natural ligands for the PBR
receptor which are produced by fermentation are
20 described below with their activity.

A screening carried out on microorganism
extracts performed on solid or liquid medium made it
possible to select three strains of microorganisms
(microscopic fungi and bacteria).

25 The three strains selected after various
studies performed to optimize the conditions for
producing significant amounts of culture extracts
having good activities in the test for measuring the

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interaction with the PBR receptor, have the references
SRL 4988, SRL 5186 and SRL 5189.

The above three strains were filed at the
CNCM of the Institut Pasteur: date of 27 August 1999
5 with the respective serial numbers I-2305, I-2306 and
I-2307.

The strain SRL 4988 classified as *Nocardia*
species, isolated from a soil sample, has the following
ecologico-physiological properties, determined after
10 culturing for two weeks at 28°C on ISP2 medium:
negative phototroph, chemo-organotroph, mesophile and
negative halophile. It is immobile and has open, non-
verticillate whorls.

The strain SRL 5186 classified as
15 *Streptomyces species*, isolated from a soil sample, has
the following ecologico-physiological properties,
determined after culturing for two weeks at 28°C on
ISP2 medium: negative phototroph, chemo-organotroph,
mesophile and negative halophile. It is immobile and
20 has flexible, biverticillate hyphae.

The strain SRL 5189 classified as
Actinosynnema species has the following ecologico-
physiological properties, determined after culturing
for two weeks at 28°C on ISP2 medium: negative
25 phototroph, chemo-organotroph, mesophile, negative
halophile. It is immobile and has flexible,
monoverticillar hyphae.

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These strains, and also their productive mutants, thus constitute a further subject of the invention.

After culturing on nutrient agar medium and
5 several successive subculturings which produce an abundant and pure culture, a storage batch 0 of the stock strain and then primary and secondary inoculation batches are prepared.

To do this, a spore suspension is prepared
10 from a culture on nutrient agar medium in a Petri dish and from an uptake medium; this medium contains a cryoprotective agent to ensure good viability of the spores during the storage by freezing.

The spore suspension obtained is distributed
15 into cryotubes which will be stored at -80°C : these tubes constitute batch 0.

By following the same protocol, but using a tube from batch 0, a primary inoculation batch is prepared. Next, again according to the same protocol, a
20 secondary inoculation batch is prepared from a primary inoculation cryotube. Manufacture of the inoculation batches 0, 1 and 2 ensures long-lasting availability of the strain and thus of the desired activity. The culturing of these three strains for obtaining natural
25 ligands of the PBR receptor may be carried out in a similar manner with the usual aerobic culture means, i.e. liquid media in fermenters of any volume with in-line monitoring of the pH and the aeration.

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EXAMPLE A SRL 4988

As an example of culturing in conical flasks for the strain SRL 4988: a secondary inoculation tube is used to inoculate Petri dishes prepared with a medium for promoting actinomycetes sporulation according to the composition:

Glucose	20 g
Soyoptim (SIO)	10 g
CaCO ₃ (OMYA)	3 g
Agar type E	20 g
Distilled water qs	1 l

The cultures are incubated in dishes for 5 days at 28°C. A spore suspension is then obtained by adding 10 ml of a liquid medium of the composition below to each Petri dish:

Glucose	30 g
Soyoptim (SIO)	10 g
Tryptone U.S.P. (Biokar)	4 g
Yeast extract (Difco)	8 g
NaCl	2.5 g
CaCO ₃	5 g
Casein hydrolyzate	5 g
Soybean papain peptone	5 g

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the pH of which is adjusted to 7.0 before sterilization.

5 ml of the spore suspensions are used to inoculate sterile 250 ml flasks, containing 50 ml of the same medium, which constitute the precultures, incubated in a warm chamber at 28°C on a shaker with shelves, or in an autonomous incubator, the rotation speeds in either of the systems being set at 210 rpm.

After shaking for two days, the preculture 10 flasks are used to inoculate the actual culture flasks at a rate of 5 ml of preculture medium per 500 ml conical flask containing culture medium (100 ml) having the composition:

Glycerol	10 g
Soluble starch	30 g
Soyoptim	15 g
Tryptone	2 g
Yeast extract	5 g
CaCO ₃	5 g
Trace element solution	10 ml
Water qs	1 l
pH 7	

15

Composition of the trace element solution used:

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$\text{FeSO}_4 \cdot 7 \text{H}_2\text{O}$	1.0 g
$\text{MnSO}_4 \cdot 4 \text{H}_2\text{O}$	1.0 g
$\text{CaCl}_2 \cdot 2 \text{H}_2\text{O}$	0.025 g
$\text{CaCl}_2 \cdot 2 \text{H}_2\text{O}$	0.10 g
H_3BO_3	0.56 g
$(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4 \text{H}_2\text{O}$	0.002 g
$\text{ZnSO}_4 \cdot 7 \text{H}_2\text{O}$	0.20 g
Water qs	1 l

Thus, in this specific case, five preculture
flasks were used to inoculate 40 culture flasks with
100 ml of culture medium per 500 ml conical flask,
5 which, after shaken culturing for 6 days at 28°C in a
warm chamber on a rotary shaker set at 210 rpm, give
4 liters of bacterial suspension.

The 4 liters of fermentation broth are
centrifuged several times, at a temperature of 4°C and
10 under a regime of 13 500 rpm (i.e. 27 500 × g with the
rotor used), in order to separate out the biomass, i.e.
the pellet combining the cells from the culture
supernatant consisting mainly of water from the
nutrient medium used and containing in solution
15 residues of components of the nutrient medium and also
metabolites produced and excreted by the bacterial
cells during the various phases of their growth.

The biomasses and supernatants are then
frozen at -20°C.

EXTRACTION OF THE NATURAL LIGANDS OF THE PBR RECEPTOR

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The 4 liters of thawed supernatant are placed in a 10 liter beaker. 400 g of Amberlite XAD 16 polystyrene-divinylbenzene resin (Rohm & Haas) are added to the solution. The suspension is shaken using a motor equipped with a paddle shaft, rotating at 20 rpm, for 15 hours. The solution is then filtered, the filtrate is removed and the drained resin is taken up in 1 liter of methanol. This mixture is stirred gently for 1 hour. The resin is again filtered off and retreated in an identical manner with 1 liter of methanol. During a third operation, the resin is retreated, this time with 1 liter of acetone. The drained resin is then removed and the 3 liters of combined organic solvent are evaporated to dryness in a rotary evaporator under vacuum.

The evaporation residue (17.7 g) is slurried in 50 ml of methanol, the suspension obtained is centrifuged at 3 000 rpm for 15 minutes and the settled supernatant obtained constitutes the culture supernatant extract.

This extract is tested in dilution for inhibition of the binding to the PBR receptor, and gives an activity evaluated at 1/200 (50% inhibition).

25 The combined biomasses (199 g) in a 2 liter beaker are treated, with stirring, with a mixture of 750 ml of methylene chloride and 750 ml of methanol. Stirring is continued for 15 hours at room temperature.

The suspension is then filtered and the clear solution obtained is concentrated under vacuum in a rotary evaporator. The evaporation residue (5.4 g) is then slurried in 50 ml of methanol and constitutes the biomass extract.

This extract is tested for inhibition of the binding of the PBR receptor, and gives an activity measured at $1/2200$ ($ID\ 50 = 2200^{-1}$).

EXAMPLE B SRL 5186

With the same respective protocols and media:

- agar medium for the subculturings on Petri dishes
- liquid preculture medium
- liquid production medium,

14 × 500 ml conical flasks containing 100 ml of production medium, and inoculated to 5%, are incubated at 28°C in a warm chamber on a rotary shaker rotating at 210 rpm, for 6 days.

After centrifugation and storage of the production supernants and biomasses for one to two days in a freezer at -20°C, these products are thawed before proceeding with their extraction.

The biomasses (54.9 g) are treated in a beaker, with stirring, with a mixture of 250 ml of dichloromethane and 250 ml of methanol, for ten hours.

The suspension is then filtered and the clear solution obtained is concentrated to dryness on a rotary evaporator.

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The dry residue (1.4 g) is slurried in 17.5 ml of methanol and the suspension obtained is centrifuged at 3 000 rpm for 15 minutes. The centrifugation supernatant collected constitutes the biomass extract.

This extract, evaluated in dilution on the test for inhibition of binding to the PBR receptor, gives a 50% inhibition in the test at a dilution of $1/3750$ ($ID_{50} = 3\,750^{-1}$).

160 g of XAD 16 polystyrene-divinylbenzene resin (Rohm & Haas) are added to the 1 400 ml of thawed supernatant and the suspension is stirred for 15 hours. The resin is filtered off, the filtrate is removed and the resin is retreated with 200 ml of solution containing 25% methanol in water for 3 hours.

The resin is filtered off and this second filtrate is removed. The resin then undergoes three similar treatments, two with 200 ml of methanol and the last with 200 ml of acetone. These last three filtrates are combined in a round-bottomed flask and then concentrated under vacuum on a rotary evaporator. The dry residue obtained (2.2 g) is then slurried in 17.5 ml of methanol and the solution obtained constitutes the supernatant extract.

This extract, evaluated in dilution on the test for inhibition of the binding to the PBR receptor, gives a 50% inhibition at a dilution of $1/940$ ($ID_{50} = 940^{-1}$).

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EXAMPLE C SRL 5189

With the same respective protocols and media:

- agar medium for the subculturings on Petri dishes
- liquid preculture medium
- 5 - liquid production medium,

10 × 500 ml conical flasks containing 100 ml of production medium, inoculated to 5%, are incubated at 28°C in a warm chamber on a rotary shaker rotating at 210 rpm, for 8 days.

- 10 After centrifugation and storage of the production supernants and biomasses for one to two days in a freezer at -20°C, these products are thawed before proceeding with their extraction.

- The biomasses (69.5 g) are treated in a
- 15 beaker, with stirring, with a mixture of 150 ml of dichloromethane and 150 ml of methanol, for ten hours. The suspension is then filtered and the clear solution obtained is concentrated to dryness on a rotary evaporator. The dry residue (1.5 g) is slurried in
- 20 12.5 ml of methanol and the solution obtained is centrifuged at 3 000 rpm for 15 minutes. The centrifugation supernatant collected constitutes the biomass extract. This extract, evaluated in dilution on the test for inhibition of the binding to the PBR
- 25 receptor, gives a 50% inhibition in the test at a dilution of 1/2600 ($ID_{50} = 2\ 600^{-1}$).

100 g of XAD 16 polystyrene-divinylbenzene resin (Rohm & Haas) are added to the 1 000 ml of thawed

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supernatant and the suspension is stirred for 15 hours. The resin is filtered off, the filtrate is removed and the resin is retreated with 150 ml of a solution containing 25% methanol in water, for 3 hours. The
5 resin is filtered off and this second filtrate is removed. The resin then undergoes three similar treatments, two with 150 ml of methanol and the last with 150 ml of acetone. These last three filtrates are combined in a round-bottomed flask and then
10 concentrated under vacuum on a rotary evaporator. The dry residue obtained (1.7 g) is then slurried in 12.5 ml of methanol and the solution obtained constitutes the supernatant extract.

This extract, evaluated in dilution on the
15 test for inhibition of the binding to the PBR receptor, gives a 50% inhibition at a dilution of 1/600 ($ID_{50} = 500^{-1}$).

In the compositions according to the invention, the substance which binds to PBR is
20 preferably used in an amount ranging from 0.00001 to 20% by weight relative to the total weight of the composition and in particular in an amount ranging from 0.001% to 10% by weight relative to the total weight of the composition.

25 The compositions according to the invention may be in any presentation form normally used for topical application.

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The amounts of the various constituents in the compositions according to the invention are those conventionally used in the fields under consideration and are appropriate for their presentation form.

5 For a topical application, the compositions of the invention comprise a medium which is compatible with the skin. These compositions may especially be in the form of aqueous, alcoholic or aqueous-alcoholic solutions, gels, water-in-oil or oil-in-water emulsions
10 having the appearance of a cream or a gel, micro-emulsions or aerosols, or alternatively in the form of vesicular dispersions containing ionic and/or nonionic lipids. These presentation forms are prepared according to the usual methods of the fields under consideration.

15 These compositions for topical application may in particular constitute a cosmetic or dermatological protective, treatment or care composition for the face, for the neck, for the hands or for the body (for example day creams, night creams,
20 antisen creams or oils or body milks), a make-up composition (for example a foundation) or an artificial tanning composition.

When the composition of the invention is an emulsion, the proportion of fatty substances it
25 contains may range from 5% to 80% by weight and preferably from 5% to 50% by weight relative to the total weight of the composition. The fatty substances and emulsifiers used in the composition in emulsion

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form are chosen from those conventionally used in cosmetics or dermatology.

As fatty substances which may be used in the invention, mention may be made of mineral oils (petroleum jelly), plant oils (liquid fraction of karite butter) and hydrogenated derivatives thereof, animal oils, synthetic oils (perhydrosqualene), silicone oils (polydimethylsiloxane) and fluoro oils. Other fatty substances which may also be mentioned included fatty alcohols (cetyl alcohol or stearyl alcohol), fatty acids (stearic acid) and waxes.

The emulsifiers may be present in the composition in a proportion ranging from 0.3% to 30% by weight and preferably from 0.5% to 30% by weight relative to the total weight of the composition.

In a known manner, the cosmetic or dermatological compositions of the invention may also contain adjuvants that are common in the corresponding fields, such as hydrophilic or lipophilic gelling agents, preserving agents, antioxidants, solvents, fragrances, fillers, screening agents and dyestuffs. Moreover, these compositions may contain hydrophilic or lipophilic active agents. The amounts of these various adjuvants or active agents are those conventionally used in cosmetics or dermatology, and, for example, from 0.01% to 20% of the total weight of the composition. Depending on their nature, these adjuvants or these active agents may be introduced into the fatty

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phase, into the aqueous phase and/or into the lipid vesicles.

Among the active agents which the compositions of the invention may contain, mention may
5 be made in particular of active agents which have an effect on treating wrinkles or fine lines, and in particular keratolytic active agents. The term "keratolytic" means an active agent which has desquamating, exfoliant or scrubbing properties, or an
10 active agent capable of softening the horny layer.

Among these active agents with an effect on treating wrinkles and fine lines, which the compositions of the invention may contain, mention may be made in particular of hydroxy acids and retinoids.

15 The hydroxy acids may be, for example, α -hydroxy acids or β -hydroxy acids, which may be linear, branched or cyclic, and saturated or unsaturated. The hydrogen atoms of the carbon chain may also be substituted with halogens, halogenated, alkyl,
20 acyl, acyloxy, alkoxycarbonyl or alkoxy radicals containing from 2 to 18 carbon atoms.

The hydroxy acids which may be used are, in particular, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, 2-hydroxyalkanoic acid,
25 mandelic acid, salicylic acid and the alkyl derivatives thereof, for instance 5-n-octanoylsalicylic acid, 5-n-dodecanoylsalicylic acid, 5-n-decanoylsalicylic acid, 5-n-octylsalicylic acid, 5-n-heptyloxysalicylic

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acid or 4-n-heptyloxysalicylic acid, and 2-hydroxy-3-methylbenzoic acid or alkoxylated derivatives thereof, for instance 2-hydroxy-3-methoxybenzoic acid.

The retinoids may be in particular retinoic
5 acid and derivatives thereof, retinol (vitamin A) and esters thereof such as retinyl palmitate, retinyl acetate or retinyl propionate, and salts thereof.

These active agents may be used in particular
in concentrations ranging from 0.0001% to 5% by weight
10 relative to the total weight of the composition.

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